PATENT

ATTORNEY DOCKET NO: CXU-379

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Appellants: Simionescu, et al.	)	Examiner: Preeti Kumar
Appl. No: 10/722,142	)	T.C./A.U: 1796
Filed: November 24, 2003	)	Deposit Acct. No: 04-1403
Title: Fixation Method For Bioprosthesis	)	Confirmation No: 4675
	)	Customer No: 22827

Mail Stop Appeal Brief - Patents
Honorable Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Honorable Commissioner:

Appellants submit the following Brief on Appeal in accordance with 37 C.F.R. § 41.37:

1. REAL PARTY IN INTEREST

The real party in interest in this matter is the assignee of record, Clemson University.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants or the Appellants' legal representative which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 20-21, 23-24, 28-39, and 47-53 are pending in this application, including independent claims 20, 30, and 48. All the claims involved in this Appeal are attached hereto at the Claims Appendix.

Claims 20-21, 23-24, 28-29, and 48-53 stand rejected. Claims 30-39 and 47 stand withdrawn as directed to a non-elected invention. Claims 1-19, 22, 25-27, and 40-46 have been previously cancelled. The rejections of claims 20-21, 23-24, 28-29, and 48-53 are hereby appealed.

4. STATUS OF AMENDMENTS

To the Appellants' knowledge, all amendments have been entered into the record.

5. SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment (independent claim 20) claims are directed to an implantable fixed tissue (p. 3, ll. 2-3) comprising cross-linked elastin (p. 4, ll. 18-19). Specifically, the cross-linked elastin of the implantable fixed tissue is cross-linked with a phenolic tannin cross-linking agent (p. 4, ll. 18-19; p. 10, ll. 6-7). As such, the implantable fixed tissue includes a residue of the phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue (p. 6, ll. 14-17).

In another embodiment (independent claim 48) claims are directed to an implantable fixed tissue comprising cross-linked elastin and cross-linked collagen (p. 12, ll. 12-19). Specifically, the implantable fixed tissue includes a residue of a phenolic tannin cross-linking agent bound to and cross-linking the cross-linked elastin of the fixed

tissue and also including a residue of an aldehyde cross-linking agent bound to and cross-linking the cross-linked collagen of the fixed tissue (p. 3, ll. 7-12; p. 6, ll. 14-19).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the Final Office Action, claims 20, 21, and 48 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, it was suggested that no support can be found in the specification for the inclusion of any residues being bound to the crosslinked elastin or crosslinked collagen.

In the Final Office Action, claims 20-21, 23-24, 28-29, and 48-53 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nimni, et al. '224 (U.S. Patent No. 4,378,224) in view of Nimni, et al. '539 (U.S. Patent No. 5,374,539).

In the Final Office Action, claims 20-21, 23-24, 28, and 48-52 were rejected under 35 U.S.C. §103(a) as obvious over Adkisson (U.S. Patent No. 6,645,764) in view of Asculai, et al. (U.S. Patent No. 6,444,222).

7. ARGUMENT

Appellant respectfully submits that claims 20, 21, and 48 fully comply with 35 U.S.C. §112, first paragraph and that the pending claims are patentable over the cited references.

A. Claims 20, 21, and 48 are fully supported in the specification as required by 35 U.S.C. §112, first paragraph.

To satisfy the written description requirement, a patent specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed subject matter," to ensure, e.g., that the inventor had possession of the claimed subject matter as of the desired priority date. *Lockwood*

v. American Airlines, Inc., 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

The USPTO carries the initial burden of establishing why a person skilled in the art would not recognize that the written description provides support for the claims. For instance, in order to establish that the written description requirement has not been met, it may be established that a claim element is neither adequately described in the specification, nor conventional in the art, nor known to one of ordinary skill in the art (66 Fed. Reg. 1099 (January 5, 2001)). Similarly, an application may lack adequate written description if a person of ordinary skill in the art cannot immediately envisage the claimed invention given the written description (66 Fed. Reg. 1099 (January 5, 2001)).

However, adequate showing of possession of a claimed invention can be shown using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (*Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)). In other words, there is no *in haec verba* requirement when considering claim limitations, and such limitations can be supported through express, implicit, or inherent disclosure (M.P.E.P. §2163(I)(B)). To satisfy the "written description" requirement of 35 U.S.C. § 112, first paragraph, the specification need only convey to those skilled in the art with reasonable clarity that Applicants possessed the claimed invention as of the filing date. Importantly, the subject matter of the claim need not be described literally (i.e., using the same terms) (M.P.E.P. §2163.02).

In the present case, it was suggested that no support can be found in the specification for the inclusion of any residues being bound to the crosslinked elastin or

crosslinked collagen. Appellants submit that the Office Action has failed to recognize the support that is presented throughout the specification for the claim terminology at issue. Moreover, Appellants submit that given the written description, a person of ordinary skill in the art would be informed so as to envisage the claimed invention.

I. The phrase 'residue of a phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue' as found in claims 20 and 48 is fully supported in the specification as filed as required by 35 U.S.C. §112, first paragraph.

As is known in the chemical arts, and specifically described with regard to tissue in the captioned application, the term 'cross-link' refers generally to the process of forming bonds, e.g., covalent bonds, between free, active moieties on or within tissue or between a cross-linking agent or other compound which reacts with a reactive moiety of the tissue (p. 6, ll. 14-19, ¶ [0029]).

As is also known, the term 'residue' refers to the remainder of something after removal of a part (see, e.g., definition 1 of the word 'residue' from the American Heritage Dictionary of the English Language, © 1980, provided at the Evidence Appendix, p. 41-42, herein), and, more specifically to the chemical arts, the term refers to an atom or group of atoms considered as a group or part of a molecule (see, e.g., definition 2b of the word 'residue' from The Random House Dictionary of the English Language, © 1967, provided at the Evidence Appendix, p. 43-45, herein).

As described in the captioned application, phenolic tannins can be used to fix the elastin component of a tissue (p. 3, ll. 17-18). Specifically, the fixed tissues can include elastin cross-linked by a phenolic tannin cross-linking agent (p. 4, ll. 18-19). Thus, the captioned application expressly informs the person of ordinary skill that the application is concerned with cross-linking components of a tissue, and in these specific

references, cross-linking elastin of a tissue with a phenolic tannin cross-linking agent. Thus, the person of ordinary skill to which this application is directed is familiar with the chemistry of cross-linking. The present specification is directed to the person of ordinary skill, and as such, the present specification need not expressly state what such person of ordinary skill already knows. Being familiar with the cross-linking of materials, the person of ordinary skill knows that cross-linking involves the formation of bonds between molecules and the chemistry involved in bond formation. The person of ordinary skill knows that in the formation of a cross-link one reactant molecule can be a cross-linking agent and another reactant molecule can be a polymer, such as elastin. The person of ordinary skill also knows that in the formation of a bond, individual atoms of a molecule can be lost. In addition, the specification specifically informs the person of ordinary skill in the art what those two molecules can be. The specification specifically informs the person of ordinary skill in the art that the application is concerned with fixed tissues that include cross-linking bonds formed between free, active moieties of elastin and phenolic tannin cross-linking agents. In order that the elastin be cross-linked as claimed, the phenolic tannin is bound to the elastin, i.e., there is some form of a reaction, e.g., a formation of a covalent bond, between free moieties of the elastin and the phenolic tannin. This concept is expressly disclosed in the description of cross-linking found in the application as well as being well-known to one of ordinary skill in the art. During the formation of a bond, one or more individual atoms of the molecules involved, e.g., the phenolic tannin cross-linking agent, can be lost. This is basic chemistry and does not require additional edification. That portion of a molecule that remains following the formation of the cross-link bond is properly termed a

residue. This is what is found in claim 20 and 48 with regard to elastin cross-linked with a phenolic tannin cross-linking agent and fully supported in the specification of the captioned application. Following formation of the cross-link bond, the fixed tissue will include that portion of the phenolic tannin cross-linking agent (the residue) that remains after the cross-linking reaction is complete and this residue will be bound to that which is being cross-linked, i.e., the elastin.

The structures recited in the above phrase at issue in this particular rejection, including the implantable fixed tissue, the phenolic tannin cross-linking agent, the elastin that is cross-linked with the phenolic tannin cross-linking agent, and the residue of the phenolic tannin cross-linking agent that remains in the implantable fixed tissue following the cross-linking reaction, are clearly and completely supported by the specification as required by 35 U.S.C. §112, first paragraph. Accordingly, Appellants request withdrawal of this rejection.

II. The phrase 'residue of an aldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue' as is found in independent claim 48, and the phrase 'residue of a glutaraldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue' as is found in dependent claim 21 are fully supported in the specification as filed as required by 35 U.S.C. §112, first paragraph.

As discussed above with regard to the formation of cross-link bonds between elastin and a phenolic tannin cross-linking agent, one of ordinary skill in the art to which the captioned application is directed knows the basic chemistry of cross-link bond formations. In addition, with specific regard to the formation of cross-link bonds between the collagen component of tissue and an aldehyde cross-linking agent, the captioned application itself specifically informs one of ordinary skill in the art that the

captioned application is directed to the fixation of the collagen component of a tissue with an aldehyde fixative, e.g., glutaraldehyde. For instance, at p. 3, ll. 7-12, the captioned application informs one of ordinary skill in the art that according to one embodiment, a tissue can first be fixed with a glutaraldehyde fixative, which can enhance the stabilization of the collagen component of the tissue, and subsequently be fixed with a phenolic tannin fixative. At p. 6, ll. 14-19, the captioned application informs one of ordinary skill in the art that the concept of cross-linking as found in the application refers to the formation of bonds, e.g., covalent bonds, between free, active moieties on or within tissue (e.g., collagen moieties) and a cross-linking agent (e.g., an aldehyde cross-linking agent such as glutaraldehyde) that reacts with a moiety of a tissue. The person of ordinary skill also knows that in the formation of a bond, individual atoms of a molecule can be lost. In order that the collagen be cross-linked as claimed, the aldehyde cross-linking agent must be bound to the collagen, i.e., there is some form of a reaction, e.g., a formation of a covalent bond, between the free moieties of the collagen and the cross-linking agent (see, e.g., p. 9, ll. 10-13). This concept is expressly disclosed in the description of cross-linking found in the application as well as being well-known to one of ordinary skill in the art. That portion of the crosslinking agent that remains in the fixed tissue following the formation of the cross-link bond is properly termed a residue. This is what is found in claims 48 and 21 with regard to collagen cross-linked with an aldehyde cross-linking agent, and specifically glutaraldehyde in claim 21, and fully supported in the specification of the captioned application. Following formation of the cross-link bonds, the fixed tissue will include that

portion of the cross-linking agent (the residue) that remains after the cross-linking reaction is complete.

The structures recited in the above phrase at issue in this particular rejection, including the implantable fixed tissue, the aldehyde cross-linking agent, the collagen that is cross-linked with the aldehyde cross-linking agent, and the residue of the aldehyde cross-linking agent that remains in the implantable fixed tissue following the cross-linking reaction, are clearly and completely supported by the specification as required by 35 U.S.C. §112, first paragraph. Accordingly, Appellants request withdrawal of this rejection.

B. Claims 20-21, 23-24, 28-29, and 48-53 are patentably distinct over Nimni, et al. '224 in view of Nimni, et al. '539.

Nimni, et al. '224 is directed to a coating for heart valves and other prosthetic devices. Specifically, through formation of a three-dimensional cross-linked matrix primarily composed of a calcification inhibitor covalently bound to accessible regions of the device, a substantially non-antigenic bioprosthesis with minimum calcification sites may be produced (col. 1, l. 65 – col. 2, l. 5).

The process of Nimni, et al. '224 as described from col. 2, l. 63 to col. 4, l. 2 includes:

(1) Partially cross-linking the collagen and protein-like compounds associated with collagen with a glutaraldehyde solution.

(2) Placing the tissue in a solution containing a calcification inhibitor, preferably chondroitin sulfate, though other substances including other polysaccharides, diphosphonates, phosphoproteins, dyes, and calcium chelators can be used.

(3) Adding an aliphatic diamine to the solution.

(4) Cross-linking the tissues and additives with a water-soluble carbodiimide.

(5) Removing excess reagents.

(6) Store the tissue in a neutral pH buffer solution containing glutaraldehyde.

The final solution can be supplemented with alcohol and surfactants or alcohol and formaldehyde.

In an alternative embodiment, described from col. 5, l. 67 to col. 6, l. 61, the process of Nimni, et al. '224 includes:

(1) Treat the tissue with a glutaraldehyde solution.

(2) Rinse the tissue in phosphate buffered saline.

(3) Place the tissue in a hexanediamine solution.

(4) Incubate.

(5) Transfer the tissues to a buffered saline solution that contains a water soluble carbodiimide.

(6) Incubate.

(7) Place the tissue in neutral, phosphate buffered saline for rinsing.

(8) Place the tissue in a buffered neutral saline solution that contains a sulphated polysaccharide.

(9) Incubate.

(10) Transfer the tissue to a buffered saline solution that contains a water soluble carbodiimide, and an aliphatic diamine.

(11) Incubate.

(12) Rinse.

(13) Transfer the tissue to a neutral, phosphate buffered saline solution containing an antithrombogenic agent, preferably heparin.

(14) Incubate.

(15) Add glutaraldehyde.

(16) Incubate.

(17) Transfer to a final storage, neutral, phosphate buffered solution containing glutaraldehyde, formaldehyde, and alcohol.

The methods of Nimni, et al. '224 enhance the amount of cross-linking by covalently attaching new amino groups to the structure, and allow the use of moieties such as peptide bound glutamic and aspartic acids to attach more cross-links by the carbodiimide reaction mechanism (col. 4, ll. 45-51).

The methods of Nimni, et al. '224 also provide an adequate number of cross-links to help retain the structural integrity of the implanted device, but not so many or so clustered that elasticity is lost (col. 5, ll. 55-59). Hence, Nimni, et al. '224 maintains elasticity through cross-link density and cross-links are formed with glutaraldehyde and carbodiimide. Nimni, et al. '224 also references in the background section of the patent a common stabilization technique involving treatment with tanning agents such as formaldehyde (col. 1, ll. 16-19).

Nimni, et al. '539 is directed to a method for preparing a purified collagen network. The method includes subjecting tissue to proteolytic enzymes in the presence of salt to remove not only the non-helical extensions at either end of a collagen molecule, but also cellular proteins, interfibrillar proteins, glycoproteins, residual serum proteins, and other extraneous material leaving behind the helical region of collagen

(col. 3, l. 57 – col. 4, l. 10). Specifically, Nimni, et al. '539 describes methods of preparing purified collagen (the section beginning at col. 4, l. 55) and methods of preparing purified collagen scaffolds (the section beginning at col. 5, l. 16) through the enzymatic digestion of non-collagenous remnants of the starting materials (see, e.g., claim 1).

Nimni, et al. '539 teaches that after achieving the objective of preserving the fibrillar collagen, one can crosslink the fibrillar network with tanning reagents to preserve their structure, and specifically, one can crosslink with bifunctional reagents such as glutaraldehyde (col. 4, ll. 18-30).

I. A person of ordinary skill in the art, having common sense at the time of the invention, would not have reasonably looked to Nimni, et al. '539 for combination with Nimni, et al. '224 as suggested in the Office Action.

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. See *In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Furthermore, "'there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness'... [H]owever, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Accordingly, even if all elements of a claim are disclosed in various prior art references, the claimed invention taken as a whole cannot be said to be obvious without some reason given in the prior art why one of ordinary skill would have been prompted

to modify the teachings of the references to arrive at the claimed invention. See e.g., *In re Regel*, 188 U.S.P.Q. 132 (C.C.P.A. 1975).

1. Nimni, et al. '224 and Nimni, et al. '539 teach away from the suggested combination.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Appellants respectfully submit that the Patent Office has failed to establish a *prima facie* case of obviousness as was suggested in the Final Office Action for at least the reason that Nimni, et al. '224 and Nimni, et al. '539 themselves teach away from the suggested combination.

As described above, Nimni, et al. '539 is directed to a process that generates a purified network of collagen. More specifically, the *essence* of the discovery of Nimni, et al. '539 is *specifically described* as the ability to retain the native collagenous framework in its 3-dimensional array devoid of surrounding non-collagenous materials (col. 3, ll. 6-9). Nimni, et al. '539 *requires* the removal of extraneous material from a starting tissue and provides a finished material that contains nothing but the purified collagen. This is the essence of Nimni, et al. '539. According to Nimni, et al. '539, the collagen remaining following removal of all other endogenous tissue components can be crosslinked, for instance with a glutaraldehyde cross-linking agent.

Nimni, et al. '224, on the other hand, provides a cross-linked tissue that introduces cross-links that are different than those created when glutaraldehyde is used alone (col. 4, ll. 39-42). More specifically, the methods of Nimni, et al. '224 covalently link endogenous polyanions (and specifically endogenous sulfated polysaccharides such as chondroitin sulfate) to collagen or some other primary structural component of

the device and then cross-link the entire structure (col. 4, l. 63 – col. 5, l. 7). In fact, Nimni, et al. '224 teaches not only the covalent linkage of these endogenous polyanions, but also the addition of extraneous calcification inhibitors (col. 5, ll. 8-10).

This is in direct contrast with what is *required* in Nimni, et al. '539. Nimni, et al. '539 *requires* the removal of all extraneous material from a tissue save the collagen; this is described as the very *essence* of the patent. Nimni, et al. '224, on the other hand, utilizes additional cross-linking materials, in addition to the traditional glutaraldehyde agent, to establish new and different covalent linkages that will not only retain non-collagenous endogenous material within the tissue, but will also bind additional extraneous materials within the tissue.

The requirements of Nimni, et al. '224 and those of Nimni, et al. '539 directly contradict each other and the references themselves teach away from the combination suggested in the Final Office Action. Nimni, et al. '539 requires removal of all non-collagenous materials while Nimni, et al., '224 retains endogenous and adds extraneous non-collagenous materials to the tissue, and these teachings directly contradict one another and teach away from combination with one another. Accordingly, Appellants respectfully request withdrawal of this rejection for at least the reason that the references teach away from the suggested combination and as such, the factual basis required to support the legal conclusion of obviousness has not been established.

II. Even if combined, Nimni, et al. '224 and Nimni, et al. '539 fail to teach limitations of the claims.

To establish a *prima facie* case of obviousness, in addition to other requirements, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. 8th Ed., Rev. 2, §2141.02, citing *W.L. Gore & Associates v Garlock, Inc.,* 721 F.2d 1540 (Fed. Cir. 1983).

In addition, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art" (*In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

1. Neither Nimni, et al. '224 nor Nimni, et al. '539, taken alone or in any proper combination, disclose or suggest a phenolic tannin cross-linking agent as is found in independent claim 20 and independent claim 48.

a. Nimni, et al. '224 does not disclose or suggest a phenolic tannin cross-linking agent as is found in independent claim 20 and independent claim 48.

Nimni, et al. '224 teaches that formaldehyde is a known tanning agent used in common stabilization techniques (col. 1, ll. 16-19) and discloses glutaraldehyde as a well known cross-linking agent (col. 1, ll. 19-20). In addition, Nimni, et al. '224 discloses a water-soluble carbodiimide cross-linking agent that forms peptide bonds by activation of carboxyl groups to allow reaction with amino groups (col. 3, ll. 45-48), and specifically, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide HCl (col. 3, ll. 53-55). These are the only specific materials disclosed in Nimni, et al. '224 as cross-linking agents.

All words must be considered in judging the patentability of a claim against the prior art and Nimni, et al. '224 simply does not disclose or suggest phenolic tannin cross-linking agents as are found in the captioned application.

Moreover, when Nimni, et al. '224 is considered in its entirety, as required, it is clear that mentions of tanning, tanning agents, etc., within the patent refer to tissues treated with aldehyde tanning agents, and do not encompass phenolic tannins as are found in the captioned application.

With regard to terms encompassing tanning, Nimni, et al. '224 discloses that a common stabilization technique involves treatment with tanning agents such as formaldehyde (col. 1, ll. 17-19). In addition, Nimni, et al. '224 teaches that the disclosed treatment is useful for rendering animal connective tissue less likely to initiate calcification than natural tissue or tanned tissue (col. 2, ll. 37-41), and tanned tissue is referred to in several of the claims (claims 1, 48, 50, 52, 54, 64). Nimni, et al. '224 also discloses that some sulfated polysaccharides, such as endogenous chondroiten sulfate, can be bound to collagen during the tanning procedure, but these polyanions are usually degraded by the host and subsequently removed from the graft (col. 4, ll. 63-67). There are no other references to tanned tissue, tanning procedures, or tanning agents in Nimni, et al. '224 and there is nothing in these references or elsewhere in the patent to lead one to the conclusion the references refer to anything but aldehyde tanning agents.

For instance, formaldehyde is a known aldehyde tanning agent and is not a phenolic tannin. Additionally, throughout Nimni, et al. '224 the disclosed treatment protocols are compared to previously known treatments in which glutaraldehyde, another aldehyde tanning agent, was utilized alone. For instance, at col. 1, ll. 23-26, Nimni, et al. '224 discloses that glutaraldehyde preserved implantations can elicit significant host reactions including calcification, while at col. 2, ll. 37-41, Nimni, et al.

'224 teaches that the disclosed treatment renders tissues less likely to initiate calcification than tanned tissue. One of ordinary skill in the art would understand, given the disclosure, that the tanned tissue that is mentioned, i.e., the tanned tissue that is more likely to initiate calcification, is the glutaraldehyde preserved tissue referred to earlier in Nimni, et al. '224.

The reference to a tanning procedure at col. 4, ll. 63-67 of Nimni, et al. '224 is also utilized in reference to calcification of tissues. Specifically, Nimni, et al. '224 states that sulfated polysaccharides can be bound to collagen during the tanning procedure, but these polyanions are usually degraded and subsequently removed from the graft and as a result this tanned material is more susceptible to calcification (col. 4, ll. 63 – col. 5, l. 3). The information provided in the Background section of Nimni, et al. '224 teaches that glutaraldehyde treatment preserved implantations can elicit a calcification response. Accordingly, the inference is again that the tanning procedure referred to in this section of Nimni, et al. '224, i.e., the procedure that provides tissue that is more susceptible to calcification, is the glutaraldehyde procedure as is common in the art and previously discussed.

When Nimni, et al. '224 is considered in its entirety, it is clear that the tanning agents and tanning procedures referred to are aldehyde tanning agents and procedures, and specifically, formaldehyde and glutaraldehyde agents and procedures. Nimni, et al. '224 simply does not disclose or suggest phenolic tannin cross-linking agents, as is required in the independent claims.

b. Nimni, et al. '534 does not disclose or suggest a phenolic tannin cross-linking agent as is found in independent claim 20 and independent claim 48.

Similar to Nimni, et al. '224, Nimni, et al. '534 does not disclose or suggest phenolic tannin cross-linking agents as are found in the pending claims.

In the Background section of Nimni, et al. '534, mention is made of explanting and crosslinking areas of an animal, such as porcine heart valves, with agents such as glutaraldehyde or other cross-linking reagents (col. 1, ll. 63-68). Thus, Nimni, et al. '534 clearly discloses glutaraldehyde as a cross-linking agent.

Claim 9 of Nimni, et al. '539 reads as follows, "[t]he method of claim 7 where the cross-linking agent is natural tannin." However, no further description as to the meaning of the term 'natural tannin' as is in this claim is contained in the description of Nimni, et al. '539. Specifically, no description as to this term encompassing a phenolic tannin as is found in the captioned application is contained in the description of Nimni, et al. '539.

Similarly, claim 8 of Nimni, et al. '539 reads, "[t]he method of claim 7 where the cross-linking agent is a salt of chromium." Again, however, no further description as to the meaning or specific agents encompassed by claim 8 is contained in the description of Nimni, et al. '539.

There are two references to tanning in the written description portion of Nimni, et al. '539. In the paragraph beginning at col. 1, l. 63 Nimni, et al. '534 states that some of the substances found in implants are not as readily tanned as collagen (col. 2, ll. 4-5). Previously in this same paragraph, glutaraldehyde is mentioned as a cross-linking agent as are 'other cross-linking reagents.' However, no additional description is provided as to what encompasses tanning agents or what other cross-linking reagents are

encompassed in the concept. Specifically, a phenolic tannin cross-linking agent is not mentioned as an agent that can provide a tanned material.

Nimni, et al. '534 also mentions tanning reagents in the paragraph at col. 4, ll. 11-30. Specifically, Nimni, et al. '539 states that one can crosslink the collagenous fibrillar network with tanning reagents to preserve their structure, but again, no additional clarification is provided. Later in that same paragraph, however, Nimni, et al. '539 states that such matrices are crosslinked with bifunctional reagents such as glutaraldehyde. Thus, the only specific agent mentioned in this paragraph that could be construed as referring to tanning reagents is the commonly known aldehyde tanning agent, glutaraldehyde. These are the only references found to tanned tissue, tanning reagents, etc. in the written description portion of Nimni, et al. '539.

There is simply no description provided as to what is intended by the claim term 'natural tannin' as is found in Claim 9 of Nimni, et al. '539. Moreover, there is no suggestion that the term encompasses a phenolic tannin cross-linking agent, as is found in the captioned application.

Accordingly, as with Nimni, et al. '224, Nimni, et al. '539 fails to disclose or suggest any phenolic tannin cross-linking agents. All words must be considered in judging the patentability of a claim against the prior art. In the present case, Appellants submit that the word 'phenolic' in the term 'phenolic tannin crosslinking agent' has not been properly considered. Nimni, et al. '539 simply does not disclose phenolic tannin cross-linking agents as are found in the captioned application.

Accordingly, even were the references to be combined as was suggested in the Final Office Action, the combined references would still fail to disclose or suggest a

phenolic tannin cross-linking agent as is found in the pending claims. For at least this reason, Appellants request withdrawal of the rejection.

2. Neither Nimni, et al. '224 nor Nimni, et al. '539, taken alone or in any proper combination, disclose or suggest an implantable fixed tissue including a residue of a phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue as well as including a residue of an aldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue as is found in independent claim 48 and dependent claim 21.

In the Final Office Action, it was stated that Nimni, et al. '224 does not teach crosslinking with the claimed phenolic tannin and recites tanning agents in general. In addition, it was stated that Nimni, et al. '539 discloses bifunctional crosslinking reagents such as natural tannins and glutaraldehyde. In addition, it was stated that it would have been obvious to combine the teachings of Nimni, et al. '224 with that of Nimni, et al. '539 because both references teach the analogous art of stabilizing heart valve implant tissue with tanning agents. However, Appellants submit that even if combined, the combined references would still fail to disclose two cross-linking agents, the first a phenolic tannin cross-linking agent bound to and cross-linking the elastin of a fixed tissue and the second an aldehyde cross-linking agent bound to and cross-linking the collagen of a fixed tissue, as is required in dependent claim 21 and independent claim 48.

As discussed above, Nimni, et al. '224 discloses the utilization of two cross-linking agents. The first is a glutaraldehyde agent, which crosslinks the collagen component of the tissue. The second is a carbodiimide cross-linking agent, which cross-links the calcification inhibitor polyanions as well as aliphatic diamines added to the tissue. Nimni, et al. '539 discloses a purified collagen network that can be cross-

linked with a tanning reagent, with glutaraldehyde specifically disclosed, and natural tannin (claim 9) or a chromium salt (claim 8) provided as alternatives. Nimni, et al. '539 does not, however, teach a combination of crosslinking agents to provide a material including different components cross-linked in a tissue.

While the Final Office Action is not clear, Appellants' understanding is that the suggested modification of the primary reference Nimni, et al. '224 is to utilize the natural tannins as taught by Nimni, et al. '539 as the tanning agent for cross-linking collagen in forming the materials of Nimni, et al. '224. However, (and ignoring for this particular argument the fact that Nimni, et al. '539 provides no information that would correlate the term 'natural tannin' with the claimed phenolic tannin cross-linking agents), even should this modification be carried out, the combination would still fail to meet the limitations of claims 48 and 21. If combined in this fashion, the fixed tissue thus formed would be crosslinked by the natural tannin crosslinking reagent of Nimni, et al. '224 and the carbodiimide crosslinking agent of Nimni, et al. '539. The material formed according to this combined teachings of references, while now including a natural tannin cross-linking agent in combination with the carbodiimide crosslinking agent, would no longer include the glutaraldehyde cross-linking agent. Thus, the combined references would still be missing a component of claims 48 and 21, i.e., the residue of the aldehyde cross-linking agent bound to and cross-linking collagen of the implantable tissue.

The references, taken alone or in any proper combination simply do not disclose or suggest the utilization of two different cross-linking agents, the first of which is a phenolic tannin cross-linking agent that cross-links the elastin of the tissue and the second of which is an aldehyde cross-linking agent that cross-links the collagen of the

tissue, as is found in claims 48 and 21. For at least this reason, Appellants request withdrawal of the rejection.

3. Neither Nimni, et al. '224 nor Nimni, et al. '539, taken alone or in any proper combination, disclose or suggest a tannic acid cross-linking agent as is found in dependent claims 24 and 51.

Neither Nimni, et al. '224 nor Nimni, et al. '539 disclose an implantable fixed tissue including a residue of a phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue in which the phenolic tannin cross-linking agent is tannic acid, as is found in dependent claims 24 and 51.

The only specific cross-linking agents disclosed in Nimni, et al. '224 and Nimni, et al. '539 are discussed above. Specifically, Nimni, et al. '224 discloses formaldehyde, glutaraldehyde, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide HCl. Nimni, et al. '539 discloses glutaraldehyde as a cross-linking agent and a general reference to natural tannins and chromium salts. Neither of the references, however, discloses tannic acid as a cross-linking agent.

III. Only improper hindsight gained from exposure to Appellants' disclosure would lead the person of ordinary skill from Nimni, et al. '224 and Nimni, et al. '539 to the limitations of claims 20-21, 23-24, 28-29, and 48-53.

Plainly, the Examiner's only incentive or motivation for modifying Nimni, et al. '224 using the teachings of Nimni, et al. '539 in the manner suggested in the Final Office Action to arrive at the rejected claims results from using Appellants' disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103.

The U.S. Supreme Court has reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument

reliant upon ex post reasoning." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d at 1397. See also, Graham v. John Deere Co., 383 U.S. at 36, 148 USPQ at 474. Nevertheless, in KSR the Supreme Court also qualified the issue of hindsight by stating that "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d at 1397.

Only with Applicants' specification could the structure of independent claims 20 and 48 be attained. For instance, the only teaching with regard to the utilization of a phenolic tannin cross-linking agent for cross-linking the elastin component of an implantable tissue can be found in the Appellants' specification. In addition, the only teaching directed to utilization of two different cross-linking agents, the first being a phenolic tannin cross-linking agent that cross-links the elastin component of an implantable tissue and the second being an aldehyde cross-linking agent that cross-links the collagen component of an implantable tissue, can be found in the Appellants' specification. Accordingly, it is respectfully submitted that the suggested modifications of the cited references relies on the impermissible use of hindsight, which cannot be successfully used to support a *prima facie* case of obviousness, and Appellants request withdrawal of the rejection.

C. Claims 20-21, 23-24, 28, and 48-52 are patentably distinct over Adkisson in view of Asculai, et al.

Adkisson describes neocartilage formations useful as implants and replacement tissue (Abstract). The neocartilage has multiple layers of cells surrounded by a substantially continuous insoluble glycosaminoglycan and collagen-enriched hyaline extracellular matrix. The neocartilage is produced *in vitro* by growing chondrocytes in

substantially serum-free growth media (col. 1, ll. 18-30). The specific attributes of the neocartilage are described from col. 3, l. 64 to col. 4, l. 11. Specifically, the neocartilage is characterized by one or more of the following attributes:

> "containing membrane phospholipids enriched in Mead acid, containing membrane phospholipids depleted in linoleic or arachidonic acid, being substantially free of endothelial, bone and/or synovial cells, having a S-GAG content of at least about 400 mg/mg of OH-proline, being substantially free of type I, III and X collagen, containing a matrix substantially free of biglycan, being enriched in high molecular weight aggrecan, being produced *in vitro* using serum-free growth medium, being essentially free of non-cartilage material, and being characterized by having multiple layers of cells surrounded by a substantially continuous insoluble glycosaminoglycan and collagen-enriched hyaline extracellular matrix"

To examine the efficacy of the neocartilage materials, implantable, sterile *in vitro* grown neocartilage implants were produced and implanted into an experimental defect of skeletally mature New Zealand white rabbits, and the animals showed excellent tolerance of the surgical procedures (col. 18, ll. 36-59).

Adkisson also describes methods utilized in histological and biochemical assessment of the formed neocartilage. Methods employed in evaluation of the *in vitro* grown materials include fixing of the tissues with glutaraldehyde, post-fixing with osmium-tetroxide, and staining en-bloc with tannic acid and uranyl acetate (col. 6, ll. 1-4). Adkisson describes additional evaluation techniques of *in vitro* grown tissues as well. For instance, following fixing and staining, as described above, implants were extracted for analysis of cartilage specific macromolecules, which were determined to include type I collagen, type II collagen, type IX collagen, type XI collagen, and Aggrecan (col. 18, ll. 13-34, including Table III). Other evaluation techniques involved the pentachrome technique. Specifically, pentachrome stains yellow for collagen, green for proteoglycan, and black for elastin (col. 5, ll. 45-46). The pentachrome technique

failed to identify elastic fibers in the neocartilage (col. 16, ll. 27-30). The neocartilage of Adkisson does not contain elastin.

Asculai, et al. discloses a reinforced matrix membrane containing one or more scaffold-forming proteins (Abstract). For instance, the process can include incubating collagen with one or more scaffold-forming proteins (such as elastin), to form a collagen-protein suspension, lyophilizing the suspension to form a fleece-like material, and pressing the fleece-like material into sheets to form a matrix (col. 3, ll. 23-37).

The matrix is a collagen matrix (col. 5, ll. 8-9) and matrix materials include collagen, hyaluronic acid and its derivatives, homologs and analogs; polylactic and polyglycolic acids; polyethylene oxide; and mixtures thereof; fibrin; proteoglycans; proteins and sugars (col. 5, ll. 24-27). The collagen matrix is described as either a reconstituted collagen matrix (i.e., cartilage tissue treated to obtain the collagen in its virtually non-cross-linked form that is then crosslinked to reestablish collagen crosslinks) (col. 5, ll. 36-53), or the collagen matrix can be formed from recombinantly produced Type II collagen, which is substantially pure, recombinantly produced Type II collagen that is not cross-linked (col. 5, ll. 60-65). Commercially available collagen matrixes are also disclosed (col. 5, l. 66 – col. 6, l. 18). The collagen matrix can be cross-linked with a variety of cross-linking agents (col. 6, ll. 19-43).

The collagen matrix is incubated with different quantities of a scaffold forming protein such as elastin (col. 5, ll. 8-10; col. 5, ll. 54-59). The General Example beginning at col. 7, l. 42 further describes the formation process. Specifically, the collagen membrane is incubated with a suspension of elastin. The elastin can be in the form of a suspension, a colloidal dispersion, or a solution. The mixture is allowed to

coacervate for 0.5 to 80 hours. Following incubation, the suspension is lyophilized to obtain a solid. This yields a fleece-like material that is then pressed mechanically into sheets for use with cells as an implantation article.

Significantly, it should be noted that while the matrix itself can be cross-linked, the scaffold forming protein is not cross-linked. Specifically, the cross-linked collagen matrix is incubated with the scaffold forming protein to form the reinforced matrix, and the final reinforced matrix includes the cross-linked collagen matrix and the scaffold forming protein, e.g., the elastin, that has been incorporated therein. The scaffold forming protein is not cross-linked within the matrix.

I. Even if combined, the combination of Adkisson and Asculai, et al. fails to teach limitations of the claims.

To establish a *prima facie* case of obviousness, in addition to other requirements, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. 8th Ed., Rev. 2, §2141.02, citing *W.L. Gore & Associates v Garlock, Inc.,* 721 F.2d 1540 (Fed. Cir. 1983).

In addition, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art" (*In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

1. **Neither Adkisson nor Asculai, et al., taken alone or in any proper combination, disclose or suggest an implantable tissue including cross-linked elastin as is found in independent claim 20 and independent claim 48.**

   a. **Adkisson does not disclose or suggest an implantable tissue including cross-linked elastin as is found in independent claim 20 and independent claim 48.**

Adkisson describes growth and development of neocartilage, as described above. The neocartilage of Adkisson does not include elastin. For instance, Example 4 of the patent (col. 18, ll. 5-59) describes the production of neocartilage. Neocartilage was grown to day 30 and then following harvest was fixed, stained, and extracted for histological evaluation. The composition of this analyzed neocartilage is shown in Table III of the example. According to Table III, the neocartilage was primarily type II collagen, but also included type IX collagen, type XI collagen, and the proteoglycan aggrecan. The compositional analysis of the neocartilage shown in Table III does not include any elastin. In addition, in Example 2 of Adkisson, biochemical assessment of the neocartilage formation failed to identify elastic fibers in the formed tissue (col. 16, ll. 27-30). Thus, the neocartilage of Adkisson does not include elastin, as is required of the implantable tissue in the pending claims of the captioned application.

Adkisson does disclose cross-linking of the neocartilage. Specifically, during histological evaluation of the neocartilage as described at col. 6, ll. 1-4, the materials can be fixed with glutaraldehyde, which will cross-link the collagen of the neocartilage. Following fixation, the neocartilage is post-fixed with osmium tetroxide, and then stained with tannic acid and uranyl acetate. Adkisson thus describes treatment of a tissue with osmium tetroxide followed by utilization of tannic acid as a stain for preparation of

materials for electron microscopy. Osmium tetroxide and uranyl acetate are both highly toxic materials (see, e.g., MSDS for osmium tetroxide and uranyl acetate provided in the Evidence Appendix at p. 46-51 and 52-56, respectively, herein). When the reference is considered as a whole, as required, the only utilization of tannic acid disclosed by Adkisson is limited to histological evaluation techniques in conjunction with osmium tetroxide and uranyl acetate that render the materials toxic and unimplantable.

Even if the neocartilage of Adkisson included elastin, which it does not, once the tissue is post-fixed with osmium tetroxide the tissue is rendered unimplantable. In Example 4 of Adkisson (col. 18, ll. 5-60) neocartilage formed according processes described in the patent are implanted in rabbits. According to this example, neocartilage implants were also fixed and stained for histological evaluation. Thus, according to the methods described by Adkisson neocartilage implants were fixed with glutaraldehyde, post-fixed with osmium tetroxide, and then stained with tannic acid and uranyl acetate for histological evaluation. The neocartilage treated with osmium tetroxide and uranyl acetate becomes toxic, it is no longer implantable. Following this treatment, this fixed and stained material was extracted. Extraction of a tissue physically destroys the tissue. It is not physically possible that the neocartilage that was implanted in the animals can be the same neocartilage that was fixed with glutaraldehyde, post-fixed with osmium tetroxide, stained with tannic acid and uranyl acetate, and then further extracted for analysis of cartilage specific macromolecules. While Adkisson does disclose collagen-containing non-implantable materials that have been treated with tannic acid for staining purposes, Adkisson does not disclose an implantable material that has been treated with tannic acid. The implantable materials

of Adkisson have not been treated with tannic acid as the treatment protocol described by Adkisson that includes staining with tannic acid renders the neocartilage unimplantable.

b. Asculai, et al. does not disclose or suggest an implantable tissue including cross-linked elastin as is found in independent claim 20 and independent claim 48.

The reinforced matrices of Asculai, et al. can include elastin. However, as discussed above, the elastin is not cross-linked. To form the reinforced collagen matrices, the cross-linked collagen matrices are incubated with different quantities of a scaffold forming protein such as elastin (col. 5, ll. 8-9; col. 5, ll. 54-59; col. 7, ll. 44-67; Examples 3-5). The cross-linked collagen matrix is thus loaded with a scaffold forming protein such as elastin. However, the scaffold forming protein is not cross-linked. Hence, the reinforced matrix membranes disclosed by Asculai, et al. include a cross-linked collagen matrix and a scaffold forming protein such as elsatin that has been loaded into the cross-linked matrix via incubation, but the elastin is not cross-linked.

c. The combination of Adkisson with Asculai, et al. does not disclose or suggest an implantable tissue including cross-linked elastin as is found in independent claim 20 and independent claim 48.

Even if one were to combine the references as was suggested in the Final Office Action, the combined references would still fail to disclose an implantable tissue including cross-linked elastin, as is required in claims 20 and 48 of the captioned application.

For instance, if one were to take the neocartilage materials of Adkisson and incubate them in the elastin-containing solution of Asculai, et al. one may obtain a neocartilage material that includes elastin therein; however the elastin is not cross-

linked. If one were to then follow the testing procedures of Adkisson and treat this new material for histological and biochemical assessment purposes, one would fix this material with glutaraldehyde (which does not cross-link elastin), post-fix this material with osmium tetroxide (which renders the material unimplantable) and then stain this now unimplantable material with tannic acid. The result is poisoned and implantable; it is *not* an implantable tissue including cross-linked elastin, as is required in claims 20 and 48.

All words must be considered in judging the patentability of a claim against the prior art. In the present case, Appellants submit that the word 'implantable' in the term 'an implantable tissue' has not been properly considered. Neither Adkisson nor Asculai, et al., taken alone or in any proper combination, disclose or suggest an implantable tissue including cross-linked elastin as is required in independent claim 20 and 48. Accordingly, for at least this reason, Appellants request withdrawal of the rejection.

2. Neither Adkisson nor Asculai, et al., taken alone or in any combination, disclose or suggest an implantable fixed tissue including a residue of a phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue as well as including a residue of an aldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue as is found in independent claim 48 and dependent claim 21.

As discussed above, even if one were to combine the references as suggested in the Final Office Action and treat the material thus obtained for histological and biochemical assessment, i.e., prepare a neocartilage according to the teaching of Adkisson and incubate this neocartilage with the elastin-containing suspension, colloid distribution, or solution of Asculai, et al. and then treat the material with glutaraldehyde,

osmium tetroxide, uranyl acetate and tannic acid, as taught in Adkisson, the material would be rendered unimplantable due at least to the osmium tetroxide treatment.

All words must be considered in judging the patentability of a claim against the prior art. In the present case, Appellants submit that the word 'implantable' in the term 'an implantable tissue' has not been properly considered.

II. Only improper hindsight gained from exposure to Appellants' disclosure would lead the person of ordinary skill from Adkisson and Asculai, et al. to the limitations of claims 20-21, 23-24, 28, and 48-52.

Plainly, the Examiner's only incentive or motivation for modifying Adkisson using the teachings of Asculai, et al. in the manner suggested in the Final Office Action to arrive at the rejected claims results from using Appellants' disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103.

The U.S. Supreme Court has reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d at 1397. See also, Graham v. John Deere Co., 383 U.S. at 36, 148 USPQ at 474. Nevertheless, in KSR the Supreme Court also qualified the issue of hindsight by stating that "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d at 1397.

Only with Applicants' specification could the structure of independent claims 20 and 48 be attained. For instance, the only teaching with regard to an implantable tissue that includes a cross-linked elastin component can be found in the Appellants'

specification. In addition, the only teaching directed to utilization of two different cross-linking agents, the first being a phenolic tannin cross-linking agent that cross-links the elastin component of an implantable tissue and the second being an aldehyde cross-linking agent that cross-links the collagen component of an implantable tissue, can be found in the Appellants' specification. Accordingly, it is respectfully submitted that the suggested modifications of the cited references relies on the impermissible use of hindsight, which cannot be successfully used to support a *prima facie* case of obviousness, and Appellants request withdrawal of the rejection.

D. The response dated August 9, 2007 fully complied with 37 C.F.R. §1.111.

I. The response dated August 9, 2007 fully complied with 37 C.F.R. §1.111(b).

In the Final Office Action, it was suggested that the arguments in the response dated August 9, 2007 failed to comply with 37 C.F.R. §1.111(b).

37 C.F.R. §.111(b) reads as follows:

> (b) In order to be entitled to reconsideration or further examination, the applicant or patent owner must reply to the Office action. The reply by the applicant or patent owner must be reduced to a writing which distinctly and specifically points out the supposed errors in the examiner's action and must reply to every ground of objection and rejection in the prior Office action. The reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references. If the reply is with respect to an application, a request may be made that objections or requirements as to form not necessary to further consideration of the claims be held in abeyance until allowable subject matter is indicated. The applicant's or patent owner's reply must appear throughout to be a *bona fide* attempt to advance the application or the reexamination proceeding to final action. A general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references does not comply with the requirements of this section.

Specifically, it was suggested that the arguments amounted to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Appellants strongly disagree with the allegation. The response dated August 9, 2007 specifically pointed out multiple examples of how the language of the claims patentably distinguishes them from the references.

For instance, in the response filed August 9, 2007, it was pointed out that neither Nimni, et al. '224 nor Nimni, et al. '539 disclose or suggest a fixed tissue including the residue of a phenolic tannin cross-linking agent bound to and cross-linking elastin of the fixed tissue, as is required in the pending independent claims and as discussed above.

In addition, the response pointed out the combined references of Nimni, et al. '224 and Nimni, et al. '539 would still fail to disclose or suggest an implantable tissue including a residue of a phenolic tannin cross-linking agent bound to and crosslinking elastin of the tissue and also including a residue of a glutaraldehyde cross-linking agent bound to and cross-linking collagen of the fixed tissue as is found in claim 24 (the response did include a typographical error in this sentence, in that the referenced claim is properly claim 21), and as discussed above.

In addition, the response pointed out that the combined references of Nimni, et al. '224 and Nimni, et al. '539 would still fail to disclose or suggest an implantable fixed tissue including both a residue of a phenolic tannin cross-linking agent bound to and cross-linking elastin of the fixed tissue, and also including a residue of an aldehyde cross-linking agent bound to and cross-linking collagen of the fixed tissue, as is found in claim 48 and as discussed above.

In addition, the response pointed out that neither Adkisson nor Asculai, et al. disclose or suggest an implantable tissue including cross-linked elastin as is required in the independent claims and as discussed above.

In addition, the response pointed out that even if combined, the combination of Adkisson and Asculai, et al. would still fail to disclose or suggest an implantable tissue including a residue of a phenolic tannin cross-linking agent bound to and crosslinking elastin of the tissue and also including a residue of a glutaraldehyde cross-linking agent bound to and cross-linking collagen of the fixed tissue as is found in claim 24 (the response did include a typographical error in this sentence, in that the referenced claim is properly claim 21), and as discussed above.

In addition, the response pointed out that even if combined, the combination of Adkisson and Asculai, et al. would still fail to disclose or suggest an implantable fixed tissue including both a residue of a phenolic tannin cross-linking agent bound to and cross-linking elastin of the fixed tissue, and also including a residue of an aldehyde cross-linking agent bound to and cross-linking collagen of the fixed tissue, as is found in claim 48.

Appellants maintain that the response dated August 9, 2007 fully complied with C.F.R. §1.111(b).

II. The response dated August 9, 2007 fully complied with 37 C.F.R. §1.111(c).

In the Final Office Action, it was suggested that the arguments in the response filed August 9, 2007 failed to comply with 37 C.F.R. §1.111(c).

37 C.F.R. §.111(c) reads as follows:

> (c) In amending in reply to a rejection of claims in an application or patent under reexamination, the applicant or patent owner must clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. The applicant or patent owner must also show how the amendments avoid such references or objections.

Specifically, it was suggested that the arguments do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made and that the arguments do not show how the amendments avoid such references or objections.

Appellants strongly disagree.

The amendments presented in the response filed August 9, 2007 included the addition of language in independent claim 20 including 'cross-linked' with regard to the elastin of the implantable tissue and the addition of language stating that the phenolic tannin cross-linking agent is bound to and cross-linking the elastin of the fixed tissue. The amendments also included the addition of language to dependent claim 21 to the effect that the implantable fixed tissue includes a residue of the glutaraldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue. The amendment filed August 9, 2007 also included new claims 48-53. Aspects of the claims including the language added in the amendments and the new claims were specifically addressed in regard to the references cited against the claims and patentable distinctions between the claims and the references were also pointed out, as discussed above with regard to the section discussing C.F.R. §.111.1(b).

Appellants maintain that the response filed August 9, 2007 fully complied with C.F.R. §111.1(c).

E. Appellants request rejoinder of the withdrawn claims.

As a final matter, Appellants respectfully request rejoinder of withdrawn claims 30-40 to the pending application. The claims are related as subcombination/combination claims. Such claims require two-way distinctness for maintenance of a restriction requirement. Specifically, the inventions are distinct if it can be shown that a combination as claimed (A) does not require the particulars of the subcombination as claimed for patentability and (B) the subcombination can be shown to have utility either by itself or in another materially different combination (MPEP §806.05(c)). In the present instance, Applicants submit that the combination as claimed in independent claim 30 requires the particulars of the implantable fixed tissue as claimed in the subcombination of independent claim 20. Accordingly, the two-way distinctness requirement has not been met, and Applicants request rejoinder of the claims.

In the Final Office Action, it was stated that the bioprosthetic support material of withdrawn claim 30 is a distinctly different search from the implantable fixed tissue and would constitute an under search burden. However, as pointed out above, the combination claim 30 requires all of the particulars of the subcombination claim 20 in that they both require the exact same implantable fixed tissue. Accordingly, the two-way distinctness requirement for maintenance of the restriction requirement has not been met and Appellants request rejoinder of the withdrawn claims.

In conclusion, it is respectfully submitted that the claims are patentably distinct over the prior art of record and that the present application is in complete condition for allowance. As such, Appellants respectfully request issuance of the patent.

Respectfully submitted,

DORITY & MANNING,
ATTORNEYS AT LAW, P.A.

3/14/08
Date

Christina L. Mangelsen, Patent Agent
Registration No. 50,244

P.O. Box 1449
Greenville, SC 29602
Telephone: (864) 271-1592
Facsimile: (864) 233-7342

8. CLAIMS APPENDIX

1-19. (Cancelled).

20. An implantable fixed tissue comprising cross-linked elastin, wherein the cross-linked elastin of the implantable fixed tissue is cross-linked with a phenolic tannin cross-linking agent, the implantable fixed tissue including a residue of the phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue.

21. The implantable fixed tissue of claim 20, further comprising cross-linked collagen, wherein the collagen is cross-linked with a glutaraldehyde cross-linking agent, the implantable fixed tissue including a residue of the glutaraldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue.

22. (Cancelled).

23. The implantable fixed tissue of claim 20, wherein the implantable fixed tissue comprises at least about 10% elastin by weight.

24. The implantable fixed tissue of claim 20, wherein the phenolic tannin cross-linking agent is tannic acid.

25-27. (Cancelled).

28. The implantable fixed tissue of claim 20, wherein the tissue is selected from the group consisting of bovine and porcine tissue.

29. The implantable fixed tissue of claim 20, wherein the tissue is selected from the group consisting of pericardium, aortic wall, heart valve, and vena cava tissue.

30. (Withdrawn) An implantable fixed tissue comprising:

cross-linked elastin, wherein said cross-linked elastin of the implantable fixed tissue is cross-linked with a phenolic tannin cross-linking agent, the implantable

fixed tissue comprising a residue of the phenolic tannin cross-linking agent bound to and cross-linking the elastin of the fixed tissue; and

a bioprosthetic support material attached to the implantable fixed tissue.

31. (Withdrawn) The implantable fixed tissue of claim 30, in which the implantable fixed tissue has an elastin content of greater than about 10% by weight of the tissue.

32. (Withdrawn) The implantable fixed tissue of claim 30, in which the implantable fixed tissue further comprises collagen, wherein said collagen is cross-linked with a glutaraldehyde cross-linking agent, the implantable fixed tissue including a residue of the glutaraldehyde cross-linking agent bound to and cross-linking the collagen of the fixed tissue.

33. (Withdrawn) The implantable fixed tissue of claim 30, wherein the implantable fixed tissue is an anisotropic tissue.

34. (Withdrawn) The implantable fixed tissue of claim 33, wherein the anisotropic tissue exhibits greater stiffness in a first direction and greater elasticity in a second direction.

35. (Withdrawn) The implantable fixed tissue of claim 30, wherein the tissue is selected from the group consisting of pericardium, aortic wall, heart valve and vena cava tissue.

36. (Withdrawn) The implantable fixed tissue of claim 30, wherein the tissue is porcine vena cava tissue.

37. (Withdrawn) The implantable fixed tissue of claim 30, wherein the support material comprises a stent.

38. (Withdrawn) The implantable fixed tissue of claim 30, wherein the support material comprises a suture ring.

39. (Withdrawn) The implantable fixed tissue of claim 30, wherein the implantable fixed tissue is a portion of a bioprosthetic heart valve.

40-46. (Cancelled).

47. (Withdrawn) The implantable fixed tissue of claim 30, wherein the phenolic tannin cross-linking agent is tannic acid.

48. An implantable fixed tissue comprising cross-linked elastin and cross-linked collagen, the implantable fixed tissue including a residue of a phenolic tannin cross-linking agent bound to and cross-linking the cross-linked elastin of the fixed tissue, the implantable fixed tissue including a residue of an aldehyde cross-linking agent bound to and cross-linking the cross-linked collagen of the fixed tissue.

49. The implantable fixed tissue of claim 48, wherein the aldehyde cross-linking agent is glutaraldehyde.

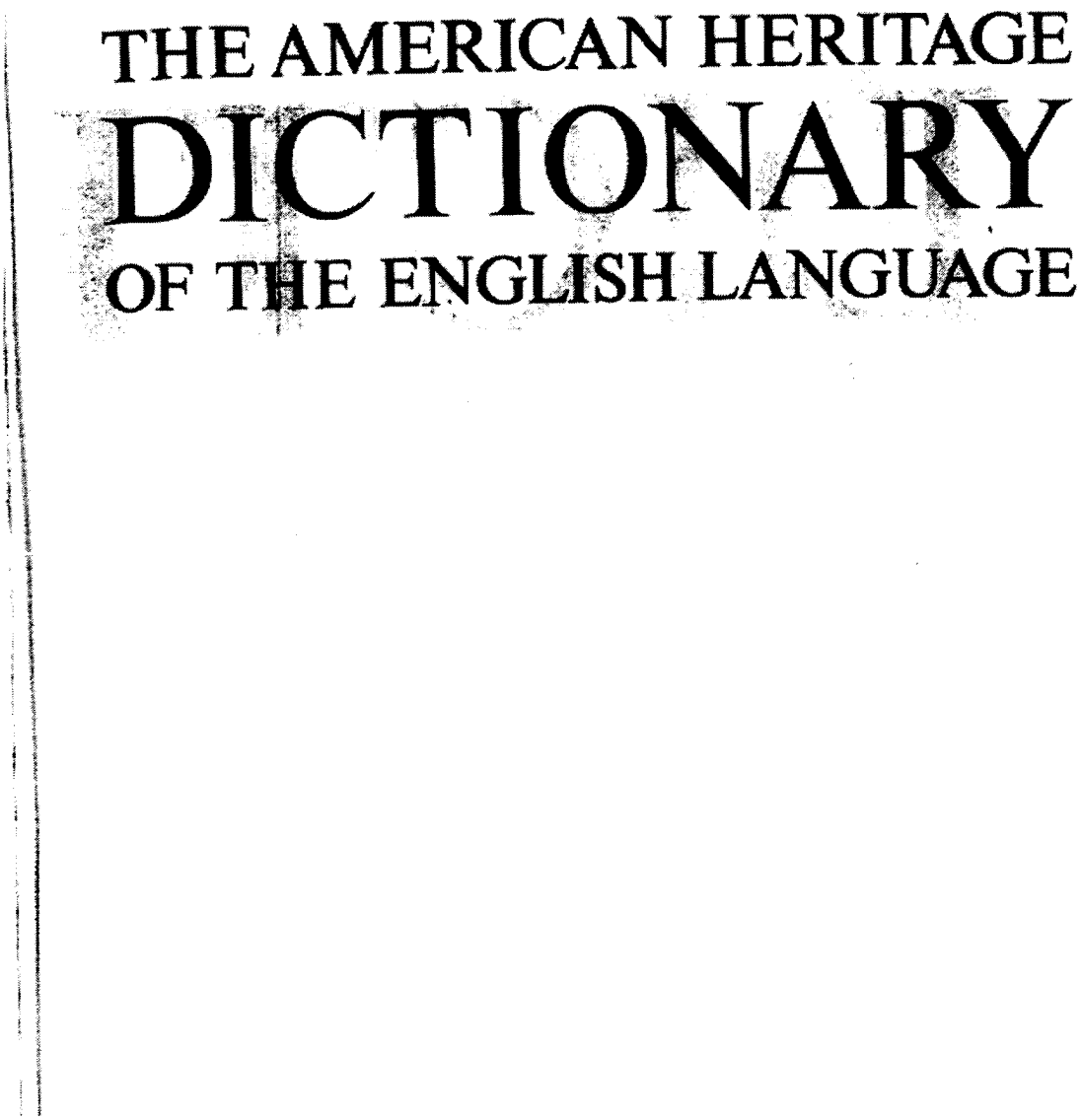
50. The implantable fixed tissue of claim 48, wherein the implantable fixed tissue comprises at least about 10% elastin by weight.

51. The implantable fixed tissue of claim 48, wherein the phenolic tannin cross-linking agent is tannic acid.

52. The implantable fixed tissue of claim 48, wherein the tissue is selected from the group consisting of bovine and porcine tissue.

53. The implantable fixed tissue of claim 48, wherein the tissue is selected from the group consisting of pericardium, aortic wall, heart valve, and vena cava tissue.

9. EVIDENCE APPENDIX



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res-i-dent (rĕz'ə-dənt, -dĕnt') *n. Abbr.* res. 1. One who makes his home in a particular place. 2. A colonial official acting as adviser to the ruler of a protected state, often having quasi-gubernatorial powers. 3. A nonmigratory bird or other animal. 4. A physician serving his period of residency. —*adj.* 1. Dwelling in a particular place; residing. 2. Living somewhere in connection with duty or work. 3. Inherently present. 4. Nonmigratory. Said of birds and other animals.

res-i-den-tial (rĕz'ə-dĕn'shəl) *adj.* 1. Of, relating to, or having residence. 2. Of, suitable for, or limited to residences.

res-i-den-ti-ar-y (rĕz'ə-dĕn'shē-ĕr'ē, -shə-rē) *adj.* 1. Having a residence, especially an official one. 2. Involving or requiring official residence. —*n., pl.* **residentiaries.** 1. A resident. 2. A clergyman required to have an official residence.

re-sid-u-al (rĭ-zĭj'ōō-əl) *adj.* 1. Pertaining to or characteristic of a residue. 2. Remaining as a residue. —*n.* 1. The quantity left over at the end of a process; remainder. 2. *Usually plural.* Payment made to a performer on a recorded television show for repeat showings. —See Synonyms at **remainder.**

re-sid-u-ar-y (rĭ-zĭj'ōō-ĕr'ē) *adj.* 1. Of, pertaining to, or constituting a residue. 2. *Law.* Entitled to the residue of an estate.

res-i-due (rĕz'ə-dōō', -dyōō') *n.* 1. The remainder of something after removal of a part. 2. Matter remaining after completion of any abstractive chemical or physical process, such as evaporation, combustion, distillation, or filtration; a residuum. 3. *Law.* The remainder of a testator's estate after all claims, debts, and bequests are satisfied. Also called "residuum." —See Synonyms at **remainder.** [Middle English, from Old French *residu*, from Latin *residuum*, from *residuus*, remaining, from *residēre*, RESIDE.]

re-sid-u-um (rĭ-zĭj'ōō-əm) *n.* 1. Something remaining after removal of a part; residue. 2. *Law.* Residue (*see*). —See Synonyms at **remainder.** [Latin, RESIDUE.]

residue

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JESS STEIN
Editor in Chief

LAURENCE URDANG
Managing Editor

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structure serving as a dwelling or home, esp. one of large proportion and superior quality: *They have a summer residence in Connecticut.* 2. the act or fact of residing: *during his residence in Spain.* 4. the act of living or staying in a specified place while performing official duties, carrying on studies or research, awaiting a divorce, etc. 5. the time during which one resides in a place: *a residence in Spain of five years.* 6. the location of the main offices or principal center of business activity of a commercial enterprise, esp. a large corporation, as registered under law. [ME < MF < ML *residentia*, equiv. to L *resid(ēre)* (to) RESIDE + *-entia* -ENCE]

—**Syn.** 1. habitation, domicile. 1, 2. See house. 2. mansion. 5. stay, abode, sojourn.

res·i·den·cy (rez′i dən sē), *n., pl.* -cies. 1. residence. 2. (formerly) the official residence of a representative of the British governor general at a native Indian court. 3. an administrative division of the Dutch East Indies. 4. the position or tenure of a medical resident. [RESIDE(NT) + -NCY]

res·i·dent (rez′i dənt), *n.* 1. one who resides in a place. 2. a diplomatic representative, inferior in rank to an ambassador, residing at a foreign court. 3. (formerly) a representative of the British governor general at a native court in India. 4. the governor of a residency in the Dutch East Indies. 5. a physician who joins the medical staff of a hospital as a salaried employee for a specified period to gain advanced training usually in a particular field, being in full-time attendance at the hospital and often living on the premises. —*adj.* 6. residing; dwelling in a place. 7. living or staying at a place in discharge of duty. 8. (of qualities) existing; intrinsic. 9. (of birds) not migratory. [< L *residen-* (s. of *residēns*), prp. of *residēre* to RESIDE; see -ENT] —**res′i·dent·ship′**, *n.*

res′ident commis′sioner, *U.S.* a representative from a dependency who is entitled to speak, but not to vote, in the national House of Representatives.

res·i·den·tial (rez′i den′shəl), *adj.* 1. of or pertaining to residence or to residences: *a residential requirement for a doctorate.* 2. adapted or used for residence: *a residential neighborhood.* [RESIDENCE + -IAL] —**res·i·den·ti·al·i·ty** (rez′i den′shē al′i tē), *n.* —**res′i·den′tial·ly**, *adv.*

res·i·den·ti·ar·y (rez′i den′shē er′ē, -shə rē), *adj., n., pl.* -ar·ies. —*adj.* 1. residing; resident. 2. bound to or involving official residence. —*n.* 3. a resident. 4. an ecclesiastic bound to official residence. [< ML *residentiāri(us)*, equiv. to *residentiā(re)* RESIDENCE + *-ārius* -ARY]

re·sid·u·al (ri zij′o͞o əl), *adj.* 1. pertaining to or constituting a residue or remainder; remaining; leftover. 2. *Math.* a. formed by the subtraction of one quantity from another: *a residual quantity.* b. (of a set) having complement of first category. 3. of or pertaining to the payment of residuals. 4. *Med.* remaining in an organ or part following normal discharge or expulsion: *residual air.* 5. *Geol.* remaining after the soluble elements have been dissolved: *residual soil.* —*n.* 6. a residual quantity; remainder. 7. Often, **residuals.** that which remains to discomfort or disable a person following an illness, injury, operation, or the like; disability: *His residuals are a weak heart and lightheadedness. She recovered with no residuals.* 8. *Math.* a. the deviation of one of a set of observations or numbers from the mean of the set. b. the deviation between an empirical and a theoretical result. 9. *Navig.* a slight deviation of an adjusted compass on a certain heading. 10. Usually, **residuals.** additional pay given to a performer by a sponsor or sponsors of a television program for repeated use of a film in which the performer appears. [< L *residu(um)* what is left over (neut. of *residuus*), equiv. to *re-* RE- + *sid-* sit (var. of *sed-*) + *-u(um)* ed). suffix + *-al*]

re·sid·u·al·ly (ri zij′o͞o ə lē), *adv.* 1. in a residual manner. 2. *Math.* with an element in the directed set such that for every element in the directed set in relation to the given element, the corresponding element of the net is in some given set; eventually. [RESIDUAL + -LY]

resid′ual stress′, *Metall.* a stress in a metal, on a microscopic scale and resulting from nonuniform thermal changes, plastic deformation, or other causes aside from temporary external forces or applications of heat.

re·sid·u·ar·y (ri zij′o͞o er′ē), *adj.* 1. entitled to the residue of an estate: *a residuary legatee.* 2. pertaining to or of the nature of a residue, remainder, or residuum. [< L *residu(um)* what is left over (see RESIDUAL) + -ARY]

res·i·due (rez′i do͞o′, -dyo͞o′), *n.* 1. that which remains after a part is taken, disposed of, or gone; remainder; rest. 2. *Chem.* a. a quantity of matter remaining after evaporation, combustion, or some other process; residuum. b. an atom or group of atoms considered as a group or part of a molecule. c. that part remaining as a solid on a filter paper after a liquid passes through in the filtration procedure. 3. *Law.* the part of a testator's estate that remains after the payment of all debts, charges, special devises, and bequests. 4. *Math.* a. the coefficient of the term with exponent −1 in a Laurent series of a function of a complex variable. b. a number related to a given number by a congruence. [ME < MF *residu* < L *residu(um)* what is left over; see RESIDUAL]

—**Syn.** 1. remains, residuum. See remainder.

residue

MSDS Number: **O5704** * * * * * *Effective Date:* ***11/02/01*** * * * * * *Supercedes:* ***11/17/99***

MSDS **Material Safety Data Sheet**

From: Mallinckrodt Baker, Inc.
222 Red School Lane
Phillipsburg, NJ 08865

Mallinckrodt CHEMICALS | J.T.Baker

24 Hour Emergency Telephone
CHEMTREC
National Response in Canada
CANUTEC
Outside U.S. and Canada
Chemtrec

OSMIUM TETROXIDE

1. Product Identification

Synonyms: Osmic acid
CAS No.: 20816-12-0
Molecular Weight: 254.20
Chemical Formula: OsO4
Product Codes:
J.T. Baker: S776
Mallinckrodt: 2768

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent	Hazardous
Osmium Tetroxide	20816-12-0	90 - 100%	Yes

3. Hazards Identification

Emergency Overview

DANGER! MAY BE FATAL IF SWALLOWED OR INHALED. CAUSES SEVERE IRRITATION TO EYES, SKIN AND RESPIRATORY TRACT.

J.T. Baker SAF-T-DATA(tm) Ratings (Provided here for your convenience)

Health Rating: 4 - Extreme (Poison)
Flammability Rating: 0 - None
Reactivity Rating: 1 - Slight
Contact Rating: 4 - Extreme (Corrosive)
Lab Protective Equip: GOGGLES; LAB COAT; VENT HOOD; PROPER GLOVES
Storage Color Code: White (Corrosive)

Potential Health Effects

Inhalation:
Coughing, choking, as well as headache and dizziness can occur. Pulmonary edema with a tightness in chest, dizziness, and cyanosis may occur after a 6 to 8 hour latent period. May cause kidney damage.
Ingestion:
Highly toxic. Severe burning pain in mouth, pharynx, and abdomen followed by vomiting and diarrhea of dark precipitated blood.
Skin Contact:
Toxic to skin. Severe pain and brownish or yellowish stains. Causes burns to skin as well as dermatitis and ulceration
Eye Contact:
Conjunctival edema and corneal destruction occur. Symptoms are pain, tearing, blurred vision (halos around lights) and photophobia. Eye effects can have insidious cumulative action with latent periods.
Chronic Exposure:
Long term exposure from inhalation can cause chronic coughs, broncho pneumonia,sterile lung abscess and gangrene.
Aggravation of Pre-existing Conditions:
Persons with pre-existing skin disorders or impaired respiratory function may be more susceptible to the effects of the substance.

4. First Aid Measures

Inhalation:
Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.
Ingestion:
Give large amounts of water to drink. Never give anything by mouth to an unconscious person. Get medical attention.
Skin Contact:
Immediately flush skin with plenty of soap and water for at least 15 minutes. Remove contaminated clothing and shoes. Get medical attention. Wash clothing before reuse. Thoroughly clean shoes before reuse.
Eye Contact:
Immediately flush eyes with plenty of water for at least 15 minutes, lifting lower and upper eyelids occasionally. Get medical attention immediately.

5. Fire Fighting Measures

Fire:
Not considered to be a fire hazard.
Explosion:
Not considered to be an explosion hazard.
Fire Extinguishing Media:
Use any means suitable for extinguishing surrounding fire.
Special Information:
Contact with oxidizable substances may cause extremely violent combustion. In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

6. Accidental Release Measures

Ventilate area of leak or spill. Wear appropriate personal protective equipment as specified in Section 8. Spills: Pick up and place in a suitable container for reclamation or disposal, using a method that does not generate dust. US Regulations (CERCLA) require reporting spills and releases to soil, water and air in excess of reportable quantities. The toll free number for the US Coast Guard National Response Center is (800) 424-8802.

7. Handling and Storage

Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from incompatible substances. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

8. Exposure Controls/Personal Protection

Airborne Exposure Limits:
-OSHA Permissible Exposure Limit (PEL):
0.002 mg/m3 (TWA) as Osmium

-ACGIH Threshold Limit Value (TLV):
0.20 ppb (TWA), 0.60 ppb (STEL) as Osmium
Ventilation System:
A system of local and/or general exhaust is recommended to keep employee exposures below the Airborne Exposure Limits. Local exhaust ventilation is generally preferred because it can control the emissions of the contaminant at its source, preventing dispersion of it into the general work area. Please refer to the ACGIH document, *Industrial Ventilation, A Manual of Recommended Practices*, most recent edition, for details.
Personal Respirators (NIOSH Approved):
If the exposure limit is exceeded and engineering controls are not feasible, wear a supplied air, full-facepiece respirator, airlined hood, or full-facepiece self-contained breathing apparatus. Breathing air quality must meet the requirements of the OSHA respiratory protection standard (29CFR1910.134).
Skin Protection:
Wear impervious protective clothing, including boots, gloves, lab coat, apron or coveralls, as appropriate, to prevent skin contact.
Eye Protection:
Use chemical safety goggles. Maintain eye wash fountain and quick-drench facilities in work area.

9. Physical and Chemical Properties

Appearance:
Colorless to pale yellow solid.
Odor:
Pungent, chlorine-like odor.
Solubility:
5.7 g/100 g water @ 10C (50F)
Specific Gravity:
4.90
pH:
No information found.
% Volatiles by volume @ 21C (70F):
0
Boiling Point:
130C (266F)
Melting Point:
ca. 40C (ca. 104F)
Vapor Density (Air=1):
8.8
Vapor Pressure (mm Hg):
7 @ 20C (68F)
Evaporation Rate (BuAc=1):
No information found.

10. Stability and Reactivity

Stability:
Stable under ordinary conditions of use and storage. Substance may react violently with some organic compounds or reducing agents.
Hazardous Decomposition Products:
When heated to decomposition, emits highly toxic fumes of osmium.
Hazardous Polymerization:
Will not occur.
Incompatibilities:
Contact with hydrochloric acid causes formation of chlorine gas. A strong catalyst and contact with easily oxidized organic materials may cause fires and explosions.
Conditions to Avoid:
Heat, dusting and incompatibles.

11. Toxicological Information

No LD50/LC50 information found relating to normal routes of occupational exposure. Investigated as a mutagen, reproductive effector.

--------\Cancer Lists\----------

Ingredient	---NTP Carcinogen--- Known	Anticipated	IARC Category
Osmium Tetroxide (20816-12-0)	No	No	None

12. Ecological Information

Environmental Fate:
When released into the soil, this material is expected to readily biodegrade. When released into the soil, this material is expected to leach into groundwater.
Environmental Toxicity:
No information found.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be handled as hazardous waste and sent to a RCRA approved waste facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Domestic (Land, D.O.T.)

Proper Shipping Name: OSMIUM TETROXIDE
Hazard Class: 6.1
UN/NA: UN2471
Packing Group: I
Information reported for product/size: .5G

International (Water, I.M.O.)

Proper Shipping Name: OSMIUM TETROXIDE
Hazard Class: 6.1
UN/NA: UN2471

Packing Group: I
Information reported for product/size: .5G

15. Regulatory Information

```
--------\Chemical Inventory Status - Part 1\---------------------------------
Ingredient                                    TSCA  EC   Japan  Australia
-----------------------------------------------  ----  ---  -----  ---------
Osmium Tetroxide (20816-12-0)                  Yes  Yes   No       Yes

--------\Chemical Inventory Status - Part 2\---------------------------------
                                                        --Canada--
Ingredient                                    Korea  DSL   NDSL  Phil.
-----------------------------------------------  -----  ---   ----  -----
Osmium Tetroxide (20816-12-0)                  Yes    Yes   No      Yes

--------\Federal, State & International Regulations - Part 1\----------------
                                          -SARA 302-     ------SARA 313------
Ingredient                                RQ    TPQ      List  Chemical Catg.
----------------------------------------  ---   -----    ----  --------------
Osmium Tetroxide (20816-12-0)             No    No       Yes         No

--------\Federal, State & International Regulations - Part 2\----------------
                                                  -RCRA-     -TSCA-
Ingredient                                CERCLA      261.33     8(d)
----------------------------------------  ------      ------     ------
Osmium Tetroxide (20816-12-0)             1000        P087       No

Chemical Weapons Convention:  No     TSCA 12(b):  No     CDTA:  No
SARA 311/312:  Acute: Yes      Chronic: Yes  Fire: No  Pressure: No
Reactivity: No          (Pure / Solid)
```

Australian Hazchem Code: 2X
Poison Schedule: None allocated.
WHMIS:
This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

16. Other Information

NFPA Ratings: Health: **4** Flammability: **0** Reactivity: **0**
Label Hazard Warning:
DANGER! MAY BE FATAL IF SWALLOWED OR INHALED. CAUSES SEVERE IRRITATION TO EYES, SKIN AND RESPIRATORY TRACT.
Label Precautions:
Do not breathe dust.
Keep container closed.
Use only with adequate ventilation.
Avoid contact with eyes, skin and clothing.
Wash thoroughly after handling.
Label First Aid:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. Remove contaminated clothing and shoes. Wash clothing before reuse. If swallowed, give large quantities of water to drink and get medical attention immediately. Never give anything by mouth to an unconscious person. In all cases, get medical attention.
Product Use:
Laboratory Reagent.
Revision Information:
MSDS Section(s) changed since last revision of document include: 8.
Disclaimer:

****

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Prepared by: Environmental Health & Safety
Phone Number: (314) 654-1600 (U.S.A.)

Material Safety Data Sheet
Product No. 19481 Uranyl Acetate, Dihydrate
Issue Date (09-04-02)
Review Date (09-20-06)

Section 1: Product and Company Identification
Product Name: Uranyl Acetate, Dihydrate
Synonym: Bis (acetato) dioxouranium, Diacetatodioxouranium, Uranium acetate, Uranium oxyacetate, Uranyl acetate, Uranyl (2+) acetate
Company Name
Ted Pella, Inc. and PELCO International, P.O. Box 492477, Redding, CA 96049-2477
Domestic Phone (800) 237-3526 (Mon-Thu. 6:00AM to 4:30PM PST; Fri 6:00AM to 4:00PM PST)
International Phone (01) (530) 243-2200 (Mon-Thu. 6:00AM to 4:30PM PST; Fri 6:00AM to 4:00PM PST)
Chemtrec Emergency Number 1-800-424-9300 24 hrs a day.

Section 2: Composition / Information on Ingredients

Principle Hazardous Component(s) (chemical and common name(s)) (Cas. No)	%	OSHA PEL mg/m3	ACGIH TLV mg/m3	NTP	IARC	OSHA regulated
*Uranyl Acetate, Dihydrate (6159-44-0)	99.9-100	0.05 (U)	NIF	NIF	NIF	NIF

***Made from Depleted Uranium**

Section 3: Hazard Identification
Emergency overview
Appearance: Solid, yellow crystals
Immediate effects: Highly Toxic, Conjunctivitis, Blood effects. Symptoms may be delayed. To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.
Potential health effects
Primary Routes of entry: Inhalation, skin absorption, ingestion.
Signs and Symptoms of Overexposure: Conjunctivitis. Blood effects. Symptoms may be delayed. To the best of our knowledge, the chemical physicals, and toxicological properties have not been thoroughly investigated.
Eyes: May cause eye irritation.
Skin: May cause skin irritation. May be harmful if absorbed through the skin.
Ingestion: May be harmful if swallowed. Target organs: Kidneys, Liver, Lungs.
Inhalation: May be harmful if inhaled. Material may be irritating to mucous membranes and upper respiratory tract.
Chronic Exposure: Carcinogen. Contains a radioactive isotope which may produce cancer or genetic mutation.

Chemical Listed As Carcinogen Or Potential Carcinogen: Yes (Radionuclides)
See Toxicological Information (Section11)
Potential environmental effects
See Ecological Information (Section 12)

Section 4: First Aid Measures
If accidental overexposure is suspected
Eye(s) Contact: In case of contact with eyes, flush with copious amounts of water for at least 15 minutes. Assure adequate flushing by separating the eyelids with fingers. Call a physician.
Skin Contact: In case of contact, immediately wash skin with soap and copious amounts of water.
Inhalation: If inhaled, remove to fresh air. If breathing becomes difficult, call a physician.
Ingestion: If swallowed, wash out mouth with water provided person is conscious. Call a physician.
Note to physician
Treatment: NIF
Medical Conditions generally Aggravated by Exposure: NIF

Section 5: Fire Fighting Measures
Flash Point: NA
Flammable Limits: NA
Auto-ignition point: NA
Fire Extinguishing Media: Water spray. Carbon dioxide, dry chemical powder, or appropriate foam.
Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
Unusual Fire and Explosion Hazards: Emits toxic fumes under fire conditions.
Hazardous combustion products: NIF
DOT Class: 7, Radioactive material, excepted package-limited quantity of material. **(Made from depleted Uranium)**

Section 6: Accidental Release Measures
Steps to be Taken in Case Material is Released or Spilled: Handle as a radioactive spill. Wear self-contained breathing apparatus, rubber boots, and heavy rubber gloves. Methods for cleaning up: Sweep-up, place in container and hold for waste disposal. Avoid raising dust. Ventilate area and wash spill site after material pickup is complete.
Waste Disposal Methods: Dispose of waste according to Federal, State and Local Regulations.

Section 7: Handling and Storage
Precautions to be Taken in Handling and Storage: User exposure: Avoid inhalation. Avoid contact with eyes, skin and clothing. Avoid prolonged or repeated exposure.
Storage temperature: Keep tightly closed. Store in a cool dry place.
Storage Pressure: NA

Section 8: Exposure Controls / Personal Protection
Engineering Controls
Ventilation required: Use only in a chemical fume hood. Use with adequate ventilation.
Personal Protection Equipment
Respiratory protection: Government approved respirator.
Protective gloves: Compatible chemical-resistant gloves
Skin protection: Suitable clothing.
Eye protection: Chemical safety goggles.
Additional clothing and/or equipment: Safety shower and eye bath.
Exposure Guidelines

See Composition/Information on Ingredients (Section2)

Section 9 Physical and Chemical Properties
Appearance and Physical State: Yellow crystals. Solid
Odor (threshold): NA
Specific Gravity (H_2O=1): 2.89 g/cm^3
Vapor Pressure (mm Hg): NA
Vapor Density (air=1): NA
Percent Volatile by volume: NA

Evaporation Rate (butyl acetate=1): NA
Boiling Point: NA
Freezing point / melting point: 110 ^{o}C
Decomposition temperature: 275 ^{o}C
pH: NA
Solubility in Water: 10% in H_2O, 20 ^{o}C soluble incomplete.
Molecular Weight: 424.15 AMU

Section 10: Stability and Reactivity
Stability: Stable
Conditions to Avoid: Protect from moisture
Materials to Avoid (Incompatibility): Strong oxidizing agents.
Hazardous Decomposition Products: Carbon monoxide, carbon dioxides, Uranium oxides.
Hazardous Polymerization: Will not occur.

Section 11: Toxicological Information
Results of component toxicity test performed: Intraperitoneal, Mouse LD50: 24 mg/Kg. Oral, Mouse LD50: 242 mg/Kg. Oral, Rat LD50: 204 mg/Kg
USA MSHA Standard-air TWA: 0.2 mg (U)/m^3
Chronic Exposure: Contains a radioactive isotope which may produce cancer and genetic mutation.
Human experience: ND
This product **does** contain compounds listed by NTP or IARC or regulated by OSHA as a carcinogen. (Radionuclides)

Section 12: Ecological Information
Ecological Information: ND
Chemical Fate Information: ND

Section 13 Disposal Considerations
RCRA 40 CFR 261 Classification: Contact a licensed professional waste disposal service to dispose of this material. Dispose of spilled material as radioactive waste. Consult local, state and federal regulations on disposal of radioactive waste. Observe all federal, state and local environmental regulations.
Federal, State and local laws governing disposal of materials can differ. Ensure proper disposal compliance with proper authorities before disposal.

Section 14: Transportation Information
US DOT Information: Proper shipping name: Radioactive material, excepted package-limited quantity of material.
Hazard Class: 7

Packaging group: None
UN Number: UN2910
Limitations: Hazard Label: None
PIH (Poison inhalation hazard): **Not** PIH
IATA: Proper shipping name: Radioactive material, excepted package-limited quantity of material
Hazard Class: 7
Packing group: None
UN Number: UN2910
Marine Pollutant: No
Canadian TDG: NIF

Section 15: Regulatory Information
United States Federal Regulations
MSDS complies with OSHA's Hazard Communication Rule 29. CFR 1910.1200.
SARA: 302.304, 313: No
SARA Title III: No
RCRA: NIF
TSCA: Listed
CERCLA: RQ as Uranyl acetate (anhydride form, CAS # 541-09-3): 100 lbs (45.4 Kg)
RTECS Number: Uranyl acetate (anhydride form, CAS # 541-09-3): YR3675000
RTECS Number: Uranyl acetate, dihydrate: YR3600000
State Regulations
California Proposition 65: This product is or contains chemical(s) known to the state of California to cause cancer. (Radionuclides)
International Regulations
Canada WHMIS: This product has been classified in accordance with the hazard criteria of the CPR, and the MSDS contains all the information required by the CPR.
DSL: Yes
NDSL: No
Europe EINECS Numbers:

Section 16: Other Information
Label Information: Highly Toxic (USA), Very Toxic (EU), Dangerous for the environment.
European Risk and Safety Phrases: R: 26/28 33 51/53. Risk Statements: Very toxic by inhalation and if swallowed. Danger of cumulative effects. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. S: 20/21 45 61. Safety Statements: When using do not eat, drink, or smoke. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). Avoid release to the environment. Refer to special instructions/safety data sheets.
European symbols needed: T+, N
US Statements: Radioactive material. Target organ(s): Liver. Kidneys.
Canadian WHMIS Symbols: NIF
HMIS(® Hazard Rating: Health: **3***; Fire: **0**; Reactivity: **0**
(0=least, 1=Slight, 2=Moderate, 3=High, 4=Extreme)
*additional chronic hazards present.
NFPA Hazard Rating: Health: **3**; Fire: **0**; Reactivity: **0**
(0=least, 1=Slight, 2=Moderate, 3=High, 4=Extreme)
Abbreviations used in this document
NE= Not established
NA= Not applicable
NIF= No Information Found

ND= No Data

Disclaimer

Ted Pella, Inc. makes no warranty of any kind regarding the information furnished herein. Users should independently determine the suitability and completeness of information from all sources. While this data is presented in good faith and believed to be accurate, it should be considered only as a supplement to other information gathered by the user. It is the User's responsibility to assure the proper use and disposal of these materials as well as the safety and health of all personnel who may work with or otherwise come in contact with these materials.

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10. RELATED PROCEEDINGS APPENDIX

None